REMARKS

Claims 1-4, 6, 8-17, and 19-24 are pending in the application and stand rejected in the final Office Action mailed February 16, 2011. In the Advisory Action mailed April 29, 2011, the Examiner indicated that the proposed amendments filed in applicant's Amendment After Final, filed April 18, 2011, would not be entered. The instant response and claim amendments supersede applicant's Amendment After Final filed April 18, 2011. In this response, Claims 1, 13, 14, 16, 17, and 21 have been amended. Claims 2 and 22 have been canceled. No new matter has been introduced. Reconsideration and allowance of Claims 1, 3, 4, 6, 8-17, 19-21, and 23-24 are respectfully requested.

Interview Summary

Applicant gratefully acknowledges the telephonic interview with Examiner Mummert on May 18, 2011. The participants in the interview were Examiner Stephanie K. Mummert and applicant's representative, Tineka J. Quinton. During the interview, the rejections of record and the prior art of record were discussed. It was noted by applicant's representative that the claimed invention is directed to the amplification and quantitation of specific target microRNA target molecules, which is not taught or suggested by any of the references of record. It was further noted that the Braash reference does not teach the use of locked nucleic acids (LNA) in the context of primers for PCR amplification, as recited in dependent Claims 2 and 22.

Agreement was not reached; however, the Examiner indicated she would reconsider the rejections of record in view of applicant's proposed amendment to incorporate the limitations of dependent Claims 2 and 22 into independent Claims 1 and 21, respectively, and further in view of applicant's written arguments for patentability of the claims as amended over the references of record.

The Rejection of Claims 1, 3-4, 6, 8, 10, 12, 15, and 19-21 Under 35 U.S.C. §103(a) as Being Obvious over Lishanski et al., in View of Lau et al., as Evidenced by Lau Supplemental Information

Claims 1, 3-4, 6, 8, 10, 12, 15, and 19-21 stand rejected under 35 U.S.C. § 103(a) as being obvious over Lishanski et al., in view of Lau et al., as evidenced by Lau Supplemental Information. Applicant respectfully traverses this ground of rejection for the following reasons.

While not acquiescing to the Examiner's position, but solely in order to facilitate prosecution, independent Claims 1 and 21 have been amended to incorporate the limitation of Claims 2 and 22, respectively, which recite "wherein at least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule."

Claims 2 and 22 have been canceled. Dependent Claims 13, 14, 16, and 17 have been amended to depend from Claim 1. No new matter has been introduced.

It is noted that Claims 2 and 22 were not included in this ground of rejection; therefore, this ground of rejection is moot with regard to the claims as amended.

The Rejection of Claims 2, 13-14, 16-17, and 22 Under 35 U.S.C. § 103(a) as Being Unpatentable over Lishanski et al., in View of Lau et al., as Evidenced by Lau Supplemental Information, and Further in View of Braasch et al.

Claims 2, 13-14, 16-17, and 22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lishanski et al., in view of Lau et al., as evidenced by Lau Supplemental Information, and further in view of Braasch et al. Applicant respectfully traverses this ground of rejection for at least the following reasons.

As noted above, independent Claims 1 and 21 have been amended to incorporate the limitations of Claims 2 and 22, which have been canceled.

The cited references, either alone or in combination, fail to render Claims 1 and 21 as amended unpatentable for at least the following reasons.

As discussed during the Examiner interview (summarized above), the claimed invention is directed to the amplification and quantitation of specific target microRNA molecules. As noted in the instant specification, microRNA molecules typically have a length in the range of from 21 to 25 nucleotides (specification at page 31-32). As further described in the specification, "Short RNA molecules are difficult to quantitate. For example, with respect to the use of PCR to amplify and measure the small RNA molecules, most PCR primers are longer than the small RNA molecules, and so it is difficult to design a primer that has significant overlap with a small RNA molecule, and that selectively hybridizes to the small RNA molecule at the temperatures used for primer extension and PCR amplification reactions." Specification at page 2, lines 20-25.

First, it is noted that none of the cited references teach or suggest a method for amplifying a specific target microRNA (Claim 1), or measuring the amount of a *specific target* microRNA in a sample from a living organism (Claim 21), comprising using an extension primer that comprises *a first portion that hybridizes to the target microRNA*, as claimed. In contrast to the claimed invention, Lishanski is generally directed toward screening for single nucleotide polymorphisms (SNPs) in genomic DNA, and is silent with regard to any miRNA analysis. The Examiner acknowledges that Lishanksi does not teach that a primer extension reaction that is carried out on a microRNA target (see final Office Action at page 7). The Examiner cites Lau et al. as teaching a method of detection of microRNA targets. However, it is noted that Lau et al. does not teach or remotely suggest a method of amplifying or quantitating a specific target microRNA using an extension primer that comprises a first portion that hybridizes to the target microRNA, as claimed. Rather, in sharp contrast to the claimed invention, the method taught in

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Lau is directed to the non-specific amplification of all microRNAs in a sample through the ligation of adaptor linkers for the express purpose of cloning previously unidentified microRNA species. In particular, Lau et al. describes the cloning of endogenous C. elegans miRNAs and the discovery of 55 previously unknown miRNAs in C. elegans. Abstract. Lau describes the construction of an amplified small RNA library by first ligating 3' RNA adaptor oligonucleotides to a pool of gel-purified 18-26 nt small RNAs from mixed-stage worms with T4 RNA ligase, gel purifying the ligated RNA, the ligating to a 5' adaptor oligonucleotide in a second T4 RNA ligase reaction, gel purifying the products from the second ligation followed by reverse transcription and PCR amplification of the linker-ligated, gel-purified products using DNA oligos corresponding to the adaptor sequences. The PCR products were then submitted for sequencing. See Footnote 23 and Lau Supplementary Materials. Moreover, it is noted that the above described cloning method of Lau could not be used for measuring the amount of a target microRNA in a sample. In contrast to the claimed methods, Lau et al. relies on the use of Northern blots for measuring microRNA expression. See pages 859 and 861, and FIGURE 3.

As acknowledged by the Examiner, Braasch is silent with regard to microRNA analysis.

Therefore, it is demonstrated that even if the teaching of Lishanski, Lau, and Braasch were to be combined, which there is no motivation to do, the combination would not result in the claimed invention because none of the references teach or suggest the use of an extension primer that comprises a first portion that hybridizes to the target microRNA, as claimed.

Second, as discussed during the interview summarized above, the cited references, either alone or in combination, do not teach or suggest the use of a method of amplifying or quantitating a specific target microRNA comprising the use of an extension primer that comprises a first portion that hybridizes to the target microRNA, "wherein at least one of the

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universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule," as recited in Claims 1 and 21 as amended.

The Examiner acknowledges that neither Lishanski nor Lau teach the use of a forward or reverse primer comprising a locked nucleic acid molecule. The Examiner cites Braasch as teaching primers and complementary sequences comprising locked nucleic acids (LNA), with reference to the Abstract, FIGURE 1, and page 6, Col. 2, of Braasch. (See page 10 of the final Office Action.) As discussed during the interview, it is noted that Braasch does not teach the use of LNA in the context of primers for PCR amplification. Rather, is noted that the Abstract refers to the use of LNA in the context of the control of gene expression and optimization of microarrays. FIGURE 1 refers to LNAs in the context of nucleic acid analogs studied for their potential as antisense agents (see Figure 1 legend), and provides the structures of such analogs, including LNA. At page 6, col 2, Braasch describes the potential use of LNA oligomers for improving DNA array technology and DNA diagnostics, such as the use of "immobilized LNAs complementary to the Factor V Leiden mutation to individual wells of a microtiter plate." It is further noted that Table 1 of Braasch, entitled "factors affecting the utility of DNA/RNA analogs and mimics," lists as the last item "ability to act as a primer" and under the comments states "necessary for applications involving polymerase chain reaction, sequencing." On page 1, Braasch states with reference to Table 1, "[T]he successful application of oligonucleotides depends on a number of factors (Table 1) and it has been estimated that up to 90% of published work using oligonucleotides to inhibit gene expression may be at least partially unreliable." Therefore, Braasch identifies the general requirements for a PCR primer to be used in connection with DNA polymerase, but does not provide any teaching or suggestion regarding the use of LNA in the context of PCR primers, or any hint or suggestion that such primers would be suitable for use in connection with DNA polymerase reactions.

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In summary, there is no teaching in Braasch regarding the use of LNA in the context of PCR primers, and as noted above, Braasch is silent with respect to microRNA analysis.

Therefore, it is demonstrated that even if the teaching of Lishanski, Lau, and Braasch were to be combined, which there is no motivation to do, the combination would not result in the claimed invention because (1) the references do not teach or suggest a method of amplifying or quantitating a specific target microRNA comprising the use of an extension primer that comprises a first portion that hybridizes to the target microRNA, and (2) the references do not teach or suggest "wherein at least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule," as recited in Claims 1 and 21 as amended. Further, no motivation exists to combine these references and there is no reasonable expectation of success to achieve the claimed invention with respect to such a hypothetical combination.

In view of the foregoing, it is demonstrated that a *prima facie* case of obviousness has not been established because Lishanski, Lau, and Braasch taken together or separately, fail to teach or suggest every limitation of Claims 1 and 21 as amended. Claims 13-14 and 16-17 depend from Claim 1. Therefore, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 9 and 11 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Lishanski in View of Lau et al., as Evidenced by Lau Supplemental Information, and Further in View of Crollius et al. and Buck et al.

Claims 9 and 11, which depend from Claim 1, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lishanski in view of Lau et al., as evidenced by Lau Supplemental Information, and further in view of Crollius et al. and Buck et al. Applicant respectfully traverses this ground of rejection for at least the following reasons.

As described above in connection with Claim 1 as amended, Lishanski and Lau, taken either together or separately, would not result in the claimed invention because (1) the references do not teach or suggest a method of amplifying or quantitating a specific target microRNA comprising the use of an extension primer that comprises a first portion that hybridizes to the target microRNA, and (2) the references do not teach or suggest "wherein at least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule," as recited in Claims 1 and 21 as amended. Further, no motivation exists to combine these references and there is no reasonable expectation of success to achieve the claimed invention with respect to such a hypothetical combination.

The teachings of Crollius and Buck fail to cure the above noted deficiencies of Lishanski and Lau. It is noted that there is no teaching or remote suggestion in Crollius with regard to a method using an extension primer that specifically hybridizes to a specific target microRNA molecule, as claimed.

Therefore, it is demonstrated that a *prima facie* case of obviousness has not been established because Lishanski, Lau, Crollius, and Buck, taken together or separately, fail to teach or suggest every limitation of Claim 1, from which Claims 9 and 11 depend. Thus, as with Claim 1 as amended, these dependent claims are also not obvious over the cited art. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 23-24 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Lishanski in View of Lau et al., as Evidenced by Lau Supplemental Information, and Further in View of Spivack et al.

Claims 23-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lishanski in view of Lau et al., as evidenced by Lau Supplemental Information, and further in

view of Spivack et al. Applicants respectfully traverse this ground of rejection for at least the following reasons.

Claims 23 and 24 depend from Claim 21. As noted above, in order to facilitate prosecution, independent Claim 21 has been amended to incorporate the limitation of dependent Claim 22, and now recites "wherein at least one of the universal forward primer and the reverse primer comprises at least one locked nucleic acid molecule."

It is noted that Claim 22 was not included in this ground of rejection; therefore, this ground of rejection is moot with regard to the claims, as amended.

Conclusion

In view of the foregoing amendments and remarks, it is submitted that all the pending claims are in condition for allowance. Reconsideration and favorable action are requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney at 206.695.1655.

Respectfully submitted,

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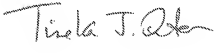

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